REMARKS

I. Status

Claims 1-16 were pending in the present application. Claims 12-16 were withdrawn from consideration. By virtue of this response, claims 8-11 have been cancelled,[1] and claims 1, 5 and 7 are amended. Accordingly, claims 1-7 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter has been added. Support for "EpoK gene product" in claim 1 is replete in the specification (see, e.g., page 10, line 3). Support for "reversible inhibitor" in claim 5 is replete in the specification (see, e.g., page 9, line 27).

II. Response

Applicants appreciate the Examiner's indication that claim 6 contains allowable subject matter. For the convenience of the Examiner, the following remarks adhere to the paragraph numbering used in the Office Action.

1. – 5. Noted.

6. The title has been amended in accordance with the suggestion by the Examiner.

7. The abstract been amended in accordance with the suggestion by the Examiner.

8a. The specification has been amended in accordance with the suggestion by the Examiner.

8b. Applicants agree that the indentation of line 26 is incorrect. Applicants request that the Examiner call the undersigned Attorney's representative to clarify whether this correction can be made by an Examiner's amendment or a whether a substitute page should be provided.

8c. Applicants respectfully disagree. Inhibitors other than metyrapone are referred to in the specification at page 35, line 10, and, in view of this, Applicants believe the text and figure are not confusing. If the Examiner still believes clarification is need, she is invited to contact the undersigned Attorney's representative to discuss possible steps.

9. Mooted by the cancellation without prejudice of claim 10.

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[1] In preliminary tests, selected compounds encompassed in claim 8 did not increase desoxyepothilone production; Applicants reserve the right to pursue the subject matter of claims 8-11 in future applications.

10. Claim 1 has been amended to specify that the microorganism is *Sorangium cellulosum*. This amendment is made without prejudice to prosecution of claims of different scope in the future.

11. Applicants believe the original language of the claims was clear. However, to expedite prosecution, Applicants have amended claim 1. Applicants believe the amendment addresses the Examiner's concern about clarity. No change in scope is intended.

12. Mooted by the cancellation without prejudice of claim 8.

13. Mooted by the cancellation without prejudice of claim 9.

14. Rejection Under 35 USC 112, First Paragraph (Written Description)

Claims 1-6 and 8 were rejected as allegedly claiming subject matter not described in the specification. The rejection is moot as to claim 8 and Applicants traverse as to claims 1-6. Applicants respectfully submit the rejection should be withdrawn for several reasons, each of which is sufficient to warrant cancellation of the rejection.

The Office states "a single example of an epothilone epoxidase inhibitor useful in the claimed methods is described." The application provides written support for numerous inhibitors (for example, original claim 7 alone provides written support for at least seven other inhibitors) and, as Applicants understand it, the Office has made no assertion that the specification does not include such support. Rather, the assertion by the Office is that, of the inhibitors described in the specification, only one is "useful." As Applicants understand it, the Office is asserting that other inhibitors would not work in the claimed method. It is respectfully submitted that this rejection is more properly a rejection under Section 101 for alleged lack of utility. Applicants believe that, as a matter of law, the Office has not presented a basis for a written description rejection.

Equally important, in articulating this rejection, the Office did not provide *any* reasoning for the assertion that inhibitors other than metyrapone would not work. Instead, the Office states "only a single species of the inhibitors is **demonstrated** [to be useful]" (emphasis added). However, it is well established that an applicant is not limited to a single exemplified embodiment, and indeed, the patent laws do not require *any* working examples.[2]

[2] For example, in *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976) the Court stated "To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred"

Thus, the Office has made no *prima facie* case for either lack of written description or lack of utility. This alone would warrant withdrawal of the rejection. To expedite prosecution, however, and without intending to be limited to particular embodiments, Applicants provide the results an assay for inhibition of EpoK activity in the table below, showing inhibition of EpoK activity by inhibitors other than metyrapone, all of which are commercially available. Of the inhibitors tested, sulconazole, miconazole and ketoconazole had the best activity.

Inhibitor	$K_{I,apparent}$ (microM)
4-Phenylimidazole	47 ± 5
Clotrimazole	4.7 ± 0.8
Itraconazole	(solubility too low for this assay)
Ketoconazole	1.7 ± 0.4
Miconazole	1.8 ± 0.7
Phenmedipham	34 ± 5
Sulconazole	0.08 ± 0.08
Sulfaphenazole	110 ± 20

In summary, Applicants maintain that the Office did not articulate a proper basis for rejection under the written description requirement, and the implied assertion of inoperativeness is incorrect. For all of the reasons above, Applicants respectfully request that this rejection be withdrawn.[3]

materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."

[3] Solely for clarity of the prosecution history, Applicants wish to record their position that the citation by the Office of the CAFC's decision in Lilly for the proposition that "[t]o adequately describe the **genus of methods** using any epothilone epoxidase inhibitors, the products themselves must be adequately described" (emphasis added) is inapposite to the present application. The *Lilly* and *Fiers* decisions relate, as the Office details, to claims to a chemical genus (i.e., compounds), not to methods which make use of a class of compounds. Applicants respectfully submit that neither of the cited cases is relevant to the present claims.

15. Rejection Under 35 USC 112, First Paragraph (Enablement)

Claims 7-11 were rejected as allegedly not supported by an enabling disclosure. This claim is moot as to cancelled claims 8-11. Applicants traverse as to claim 7.

The gist of the argument set forth in the Office Action is that "P450 enzymes are 'one of the largest superfamilies of enzyme proteins' that are 'extremely diverse' and that for this reason the use of different substrates in their diverse reactions renders generic use of general P450 enzyme inhibitors highly unpredictable in the absence of other evidence . . ." Applicants respectfully believe the conclusion drawn by the Office is not supported. The Werck-Reichhart et al. reference relied on by the Office emphasizes that the P450 family is highly conserved and that, although amino-acid sequences are diverse, there is a high conservation of general topology and structural fold, with the highest structural conservation at the core of the enzyme around the heme (see page 2, column 2[4]). Werck-Reichhart et al. note that this structural conservation reflects a *common mechanism* that has remained the same throughout evolution (see page 2, column 2).[5] This is consistent with the fact that individual inhibitors can inhibit multiple different P450 enzymes, and that individual P450 enzymes can be inhibited by multiple different inhibitors.[6] It has further been shown that azole inhibitors act by binding of an azole nitrogen atom to the iron atom of the cytochrome P450 cofactor (see, for example, Cupp-Vickery et al., 2001, "Ketoconazole-induced conformational changes in the active site of cytochrome P450eryF," *J. Mol. Biol.* 311:101-110). As the heme cofactor is a common element among P450 enzymes, there is thus a common mechanistic rationale for examining general P450 inhibitors against EpoK.

Applicants submit that one of skill would have understood that many inhibitors of other P450s would also inhibit the *epo*K gene product, and that no undue experimentation would be

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[4] The copy of the reference provided by the Office is an internet publication which did not include page numbers (certain figures and text are also missing). Applicants' reference to page numbers assumes that the first page is page number 1.

[5] A more recent publication, Nagano et al., 2003, "Crystal structures of epothilone D-bound, epothilone B-bound, and substrate-free forms of cytochrome P450epoK" J Biol Chem. 278:44886-93, provides a crystal structure of EpoK (referred to as "P450epoK") and emphasizes the structural similarities to other P450s. Copies of newly cited scientific articles will be forwarded to the Examiner under separate cover.

[6] For example 14-a-demethylase (Candida krusei) is inhibited by ketoconazole, itraconazole, fluconazole (Venkateswarlu et al., 1997, J. Med. Vet. Mycol. 35:19-25); CYP2A6 (human) is inhibited by ketoconazole, miconazole, clotrimazole, but not itraconazole or fluconazole (Draper et al., 1997, Arch Biochem. Biophys. 341:47-61); lauric acid omega-1-hydroxylase (trout) is inhibited by ketoconazole, miconazole, clotrimazole (Miranda et al., 1998, Toxicol. Appl. Pharmacol. 148:237-44).

required to identify compounds with this property. Assays for enzyme inhibition are considered highly routine in the art, and guidance for conducting an exemplary assay is provided in the specification (e.g., page 21, first paragraph). Applicants submit that such routine inhibition assays do not constitute "undue" experimentation. Applicants respectfully submit that the claims are clearly enabled.

Finally, the Office appears to suggest that the enablement requirement is not met because some inhibitors may have a detrimental effect on cell growth. Applicants respectfully submit that selection of preferred inhibitors and concentrations, expressly discussed by the inventors (see page 13 of the specification) is merely optimization and is the epitome of "routine experimentation." [7]

For all of the reasons provided above, Applicants request that this rejection be withdrawn.

[7] Further, there is no requirement that a claimed method be optimized, or even that it work "well" in a commercial sense.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 300622005700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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